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Clinical study

Increasing radiation dose intensity using hyperfractionation in patients with malignant glioma

Final report of a prospective phase I–II dose response study

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Abstract

We attempted to show a dose effect relationship for radiation therapy by treating patients harbouring malignant glioma with increasing doses of radiation in a step-wise fashion. We postulated that no increase in delayed toxicity would be seen because we used hyperfractionation technique. Between January 1981 and December 1988 we treated 280 patients three times daily at 4 hour intervals. 100 patients received a total dose of 6141 cGy, 73 patients received 7120 cGy, and 107 patients received 8000 cGy. CCNU was given at the time of tumor progression following radiotherapy. Median time to tumor progression was 28 weeks for patients who received 6141 cGy, 27 weeks for patients who received 7120 cGy and 36 weeks for patients who received 8000 cGy. Median survival was 46 weeks for patients who received 6141 cGy, 38 weeks for patients who received 7120 cGy and 45 weeks for patients who received 8000 cGy. There was no statistically significant difference in either time to tumor progression or survival among the three treatment arms and no dose response effect was seen. There was no increase in delayed radiation toxicity when the total radiation dose was increased up to 8000 cGy.

Introduction

Dose response effect

Walker *et al.* [1] concluded that a clear-cut dose-effect relationship exists in malignant glioma patients treated with radiation therapy. In patient groups otherwise comparable with respect to prognostic factors such as histology, age and performance status, increasing the dose of radiation from 5.0 Gy to 6.0 Gy significantly increased survival. Salazar *et al.* [2] retrospectively analyzed the results of radiation therapy of patients with malignant glioma treated with tumor doses up to 8.0 Gy. They found significantly longer survival in patients treated with very high dose radiation (median tumor dose 7.5 Gy) compared to lower doses. In both these studies, radiation was given by conventional, daily fractionation.

Despite these reports of the possible advantage of higher dose of radiation therapy, doses higher than 6.0 Gy are not routinely used for the treat-

ment of patients with malignant brain tumor because of the known increased incidence of unacceptable late toxicity, especially brain necrosis and dementia, at higher dose levels [3].

Hyperfractionation – theoretical advantages

Compared to standard once daily radiation therapy, hyperfractionation may be defined as the use of smaller (less than 120 cGy) radiotherapy dose fractions given more than once daily without changing the overall treatment time. Hyperfractionation may permit the delivery of higher total radiation doses without an increase in the incidence of delayed toxicity [4, 5].

In theory, the reasons for the improved outcome following radiation therapy when given using hyperfractionation are:

1. Decreasing the dose of each radiation fraction will preferentially spare normal central nervous system tissues as a result of their greater capacity for repair of sublethal injury, thus permitting the use of higher total radiation doses likely to result in greater tumor cell kill.
2. Increasing the number of fractions (and number of inter-fraction intervals) will allow more opportunities for redistribution of tumor cells into more sensitive phases of the cell cycle, thus increasing tumor cell kill [6].
3. With lower doses of radiation per fraction, tumor cell killing by radiation is less oxygen dependent [7]. In addition, with an increased number of fractions there may be a greater chance for tumor reoxygenation [8, 9]. Since malignant gliomas are known to contain areas of hypoxia, both of these factors, in theory, are likely to result in greater tumor cell kill.

Hyperfractionation – clinical experience

Several studies of hyperfractionated radiation therapy have been carried out in patients with malignant glioma. The results do not agree. Douglas and Worth [10] reported significantly longer survival in patients with malignant glioma treated with hyperfractionation compared to historical controls. Payne *et al.* [11] in a randomized prospective trial, found no improvement in survival of patients treated with hyperfractionation, but the total dose of radiation may have been too small.

Hypothesis

The purpose of this study was to test the following hypotheses:

1. Increasing the total dose of radiation of patients with malignant glioma (anaplastic astrocytoma or glioblastoma multiforme) results in improved time to tumor progression and survival.
2. Administration of higher than conventional doses of radiation using smaller fraction sizes delivered three times daily at intervals of more than four hours will not produce an increased incidence of delayed toxicity.

Materials and methods

Patient population

All patients with malignant glioma in the province of Alberta, Canada (population of 2.5 million) are referred to one of the two cancer treatment centers participating in the study. All of these patients aged between 18 and 70 with histologically proven anaplastic astrocytoma or glioblastoma multiforme and Karnofsky [12] performance score of 30 or greater were eligible to participate in the study. With very few exceptions, all agreed to participate. Patient characteristics are outlined in Table 1. Informed consent was obtained from all patients after the nature of the treatment was fully explained.

Histological review

All tumor histology was reviewed by one of the three participating neuropathologists. Anaplastic astrocytoma was diagnosed when the tumor was moderately to markedly hypercellular and when there was nuclear aplasia consisting of moderate

enlargement, moderate pleomorphism and marked hyperchromasia. Occasional tumor cells with markedly enlarged bizarre nucleus or multinucleated cells could be present but only small numbers of mitotic figures. Some of the blood vessels showed endothelial hypertrophy and hyperplasia. Necrosis was rarely seen.

Glioblastoma multiforme was diagnosed when the tumor showed markedly increased cellularity with marked nuclear anaplasia. Mitotic figures were common. Necrosis was common and often associated with pseudopallisading of tumor cells. There was blood vessel proliferation with reactive endothelial changes.

Treatment

In this dose-response study, we planned to treat patients with increasing radiation doses in a step-wise fashion. As a first step, between January 1981 and December 1982 patients were randomized to either conventional fractionation (5800 cGy, 30 fractions, 6 weeks), three times daily radiation (6141 cGy) or three times daily radiation (6141 cGy) with misonidazole (Fulton *et al.* 1984). Misonidzole was given at a dose of 1.25 gm per m^2 three times weekly for the first three weeks of treatment. In January 1983, the conventional fractionation and misonidazole arms were dropped and another arm was opened in which patients were treated three times daily to a total dose of 7120 cGy. Patients were randomized to either 6141 cGy, 6141 cGy plus misonidazole or 7120 cGy. The randomization was weighted so more patients received 7120 cGy. In January 1986, the 6141 cGy arms and the 7120 cGy arms were dropped and all patients were treated three times daily to a total dose of 8000 cGy. The study was closed to patient accrual on December 31, 1988. All patients who were treated three times daily received treatment at a minimum of 4 hour intervals as outlined in Table 2. Treatment was started within 2 weeks of surgery utilizing the Cobalt 60 unit at 80 cm SAD early on in the study and the 6MV linear accelerator at 100 cm SAD. Adequate immobilization was ensured through the use of a head shell holding device. The volume of treatment was calculated from the preoperative enhanced CT scans covering the enhancing lesion plus peritumoral edema plus a 2.5 cm margin (approximately 3/4 brain volume) for the first 4000 cGy using parallel opposing pair technique, coning down to the enhancing lesion plus 2.5 cm margin to the 90% isodose distribution using wedge pairs for the remainder of the radiation dose. The dose per fraction was 89 cGy for the first two dose steps and 100 cGy for the final dose step. The overall treat-

Table 1. Patient characteristics

	6141 cGy		7120 cGy		8000 cGy		All patients	
	N	(%)	N	(%)	N	(%)	N	(%)
Sex: male	66	(66)	43	(59)	79	(74)	188	(67)
female	34	(34)	30	(41)	28	(26)	92	(33)
Age ≤ 40	19	(19)	12	(16)	27	(25)	58	(21)
40–59	44	(44)	39	(53)	52	(49)	135	(48)
60+	37	(37)	22	(30)	28	(26)	87	(31)
Karnofsky ≥ 70	65	(65)	55	(75)	93	(87)	213	(76)
Karnofsky < 70	35	(35)	18	(25)	14	(13)	67	(24)
Biopsy only	11	(11)	9	(12)	7	(6)	27	(10)
Subtotal resection	89	(89)	64	(88)	100	(94)	253	(90)
Anaplastic astrocytoma	29	(29)	17	(23)	32	(30)	78	(27)
Glioblastoma multiforme	71	(71)	56	(77)	75	(70)	202	(73)
Total	100		73		107		280	

ment time was $4^1/_2$ weeks for the 6141 cGy group and $5^1/_2$ weeks for the 7120 and 8000 cGy groups.

CCNU chemotherapy was given at the time of tumor progression. The dose was 120 mg/m^2 every 6 weeks with adjustment for myelotoxicity.

Follow-up evaluation

All patients were evaluated prior to treatment and at three month intervals after the completion of treatment until death with neurological examinations and computerized tomographic (CT) scans. All follow-up assessments were carried out by the study physicians at one of the two cancer treatment centers participating in the study. Minimum follow-up for all patients was 120 weeks.

Criteria for tumor progression

Tumor progression was defined as increased enhancing tumor volume of CT scan and/or neurological deterioration for which no explanation other than tumor progression could be found.

Statistical methods

Survival and time to tumor progression curves were estimated according to the method of Kaplan and Meier [13] and differences in the survival and time to tumor progression estimates between groups of patients treated with different doses of radiation therapy were assessed using the log-rank test [14, 15]. P values less than 0.05 were considered significant.

The effects of selected variables – sex, age at diagnosis (< 40, 40–59, > 60), histology (anaplastic astrocytoma vs glioblastoma multiforme), Karnofsky performance score (KPS 80–100, 60–70, ≥ 50), and extent of surgery (biopsy vs resection), – on survival and time to tumor progression were assessed with the Cox proportional hazards model [16, 17]. Time to tumor progression and survival time were measured from the first day of radiation therapy.

Results

All patients

Between January 1981 and December 1988, 280 patients entered the study. Ninety-two percent completed radiation therapy according to protocol, 94 percent in the 6141 cGy arm, 93 percent in the 7120 cGy arm and 90 percent in the 8000 cGy arm. Some patients refused any chemotherapy at the time of tumor progression, however, overall 82 percent of patients received CCNU chemotherapy according to protocol, 86 percent in the 6141 cGy arm, 85 percent in the 7120 cGy arm and 76 percent in the 8000 cGy arm.

There was no significant difference in either time to tumor progression or survival (Table 3) or in long term survival (Table 4) among the three treatment arms. As shown in Figs 1 and 2, there was no consistent change in time to tumor progression or survival as the radiation dose was increased.

As previously reported [18, 19] there was no difference in time to tumor progression or survival between patients on the 6141 cGy arm who received misonidazole and those who did not. Therefore, these patients are grouped together in this report.

Effect of selected variables on survival

The selected variables of age (< 40, 40–59, ≥ 60), Karnofsky performance status (≤ 70, < 70), extent of surgery (biopsy vs resection) and histology (anaplastic astrocytoma vs glioblastoma multiforme) were studied using the Cox proportional hazards analysis, both univariate and multivariate (Table

Table 2. Radiation therapy treatment according to protocol

Total dose	No. of fractions	Fraction size	Total time
6141 cGy	69	89 cGy	$4^1/_2$ weeks
7120 cGy	80	89 cGy	$5^1/_2$ weeks
8000 cGy	80	100 cGy	$5^1/_2$ weeks

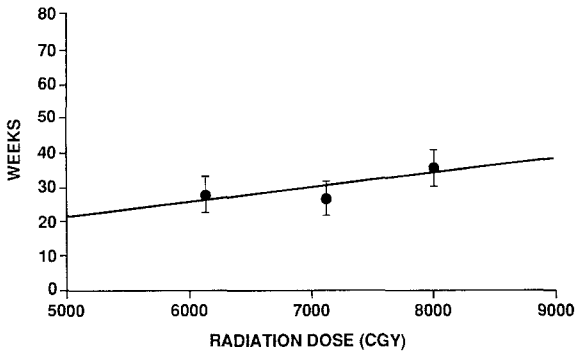

Fig. 1. Mean time to tumor progression by treatment arm. Footnote: bars indicate one standard deviation.

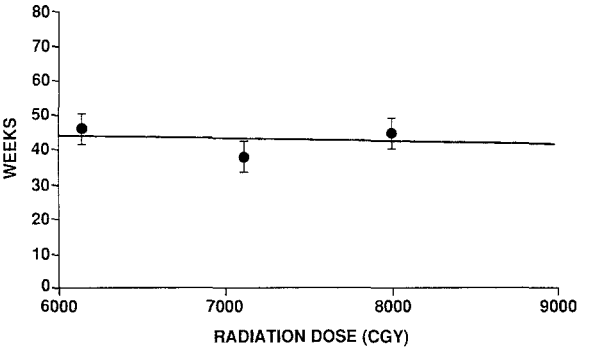

Fig. 2. Median survival by treatment arm. Footnote: bars indicate one standard deviation.

5). All were significant when studied using univariate analysis.

When the effect of these variables on survival was studied using Cox multivariate analysis, age was found to be the most significant variable ($p < 0.00005$). Karnofsky performance score and extent of surgery were of intermediate significance, histology the least significant ($p = 0.0014$).

Effects of selected variables on time to progression

When the effect of these variables on time to tumor progression was studied using Cox multivariate analysis (Table 6), age was found to be the most significant variable ($p = 0.00005$). Extent of surgery and histology were significant, but less so than age. Karnofsky performance score was not significant.

Table 3. Results for all patients according to radiation dose

	Median time to tumor progression (weeks)	Median survival (weeks)
6141 cGy	28	46
7120 cGy	27	38
8000 cGy	36	45
Tests for equivalence of Kaplan-Meier curves*	$p = 0.502$	$p = 0.414$

* Probability values are for the log rank test. Group differences are adjusted for age, Karnofsky performance score and histology. $P > 0.05$ indicates Kaplan-Meier curves are not significantly different.

Subset analysis

Comparison to Radiation Therapy Oncology Group (RTOG) Study 83-02

The Radiation Therapy Oncology Group has recently completed a randomized phase II study of hyperfractionated radiation therapy and BCNU for supratentorial malignant glioma. The study had four treatment arms. Patients were treated with 120 cGy twice daily to total doses of 6480 cGy, 7200 cGy, 7680 cGy or 8160 cGy. All patients received BCNU 80 mg per m^2 IV on days 1, 2 and 3 of radiation therapy and then BCNU 80 mg per m^2 for 3 days every eight weeks for one year. Median survivals for the four treatment groups were: 6480 cGy – 49 weeks (compared to our study 6141 cGy arm median survival of 46 weeks), 7200 cGy – 55 weeks (com-

Table 4. Results – % survival according to treatment

	% Survival				
	6141 cGy	7120 cGy	8000 cGy	All patients	GBM pts only
1 Year	41	34	47	41	33
2 Year	21	11	18	17	10
3 Year	15	7	13	12	6
4 Year	12	7	10	10	4
5 Year	7	7	–	7	3

pared to our study 7120 cGy arm median survival of 38 weeks), 7680 cGy – 52 weeks and 8160 cGy – 51 weeks (compared to our study 8000 cGy arm median survival of 45 weeks). There was no significant difference in survival among 6480 cGy, 7200 cGy and 7680 cGy arms; however, patients treated on the 8160 cGy arm were found to survive for a significantly shorter period of time [22].

To facilitate comparison between this study and our study, we examined the subset of our patients who met the criteria for entry into the RTOG study; namely, histologically proven anaplastic astrocytoma or glioblastoma multiforme, age 18 to 70 and Karnofsky performance score 60 or greater. For this subset of our patients, median survival was 52 weeks for those treated with 6141 cGy, 38 weeks for those treated with 7120 cGy and 46 weeks for those treated with 8000 cGy. These differences in survival were not significant ($p = 0.55$).

Patient groups in the two studies were very comparable regarding age distribution, KPS and the proportion of patients harboring glioblastoma multiforme.

Compliance with radiation therapy treatment was comparable in the two studies. In the RTOG study 82% of patients completed treatment according to protocol or with acceptable variations. In our study 92% completed radiation therapy according to protocol.

In the RTOG study all but 3% of patients completed chemotherapy according to protocol. In our study 18% of patients refused CCNU chemotherapy at the time of tumor progression.

Search for dose response effect

We analyzed many subgroups of patients to try to find a subgroup for which either time to tumor progression or survival varied directly with tumor dose. We examined patient groups with good prognostic factors such as young age and anaplastic astrocytoma. We examined patient groups with poor prognostic factors such as older age and glioblastoma multiforme. We also examined groups with various combinations of prognostic factors. We were unable to find a subgroup of patients in whom either time to tumor progression or survival could be directly correlated with total radiation dose.

Toxicity

Acute skin toxicity

As outlined in Table 7, the highest incidence of acute skin toxicity (65%) was observed in the group receiving the highest dose of radiation. The degree of toxicity was mild (erythema only) for most patients. Moderate toxicity (wet desquamation), mainly behind ears and in the external auditory canals, was seen in seven percent of patients in the 6141 cGy and 7120 cGy treatment arms, but in 13 percent in the 8000 cGy arm.

Table 5. Test for prognostic significance of selected variables on survival (Cox Proportional Hazards Model)

Selected variable	Multivariate analysis	Univariate analysis
Age	$p < 0.00005$	$p < 0.00005$
Karnofsky performance Score ($K \geq 70$ vs $K < 70$)	$p = 0.0001$	$p < 0.00005$
Surgery (biopsy vs resection)	$p = 0.0006$	$p = 0.0013$
Histology (anaplastic astrocytoma vs glioblastoma multiforme)	$p = 0.0014$	$p < 0.00005$
Sex	$p = 0.0366$	$p = 0.5565$

Table 6. Test for prognostic significance of selected variables on time to tumor progression (Cox Proportional Hazards Model)

Selected variable	Multivariate analysis	Univariate analysis
Age	$p < 0.00005$	$p < 0.00005$
Karnofsky performance Score ($K \geq 70$ vs $K < 70$)	not sign.	$p < 0.00005$
Surgery (biopsy vs resection)	$p = 0.0039$	$p = 0.0107$
Histology (anaplastic astrocytoma vs glioblastoma multiforme)	$p = 0.0003$	$p < 0.00005$
Sex	not sign.	$p = 0.5790$

Delayed radiation toxicity

We were concerned about the possibility of an increased incidence of radiation induced brain necrosis in those patients who received high doses of radiation. Therefore the brain of all autopsied patients were carefully searched for histological evidence of radiation damage. The overall autopsy rate was 14%.

As outlined in Table 8, histological evidence of radiation damage was seen in three of 31 autopsied patients who survived for at least 3 months after completion of radiation therapy and therefore were considered at risk for late delayed radiation toxicity. However, all three of these patients also had recurrent tumor and the radiation effect was confined to the region of the tumor. All three patients suffered neurological deterioration prior to death, but this deterioration was more likely caused by tumor growth than by radiation toxicity.

Conclusions and discussion

Dose response effect

No prolongation of time to tumor progression or survival was seen with increasing radiation dose. That is, no dose response effect was seen in our patient population. This lack of dose response effects might be explained if there was a subgroup of patients in whom increasing radiation dose produced longer time to tumor progression and survival, but also another subgroup in which time to tumor progression and suvival were shorter at higher radiation dose, perhaps because of increased toxicity. Our analysis suggests this was not the explanation for the lack of dose response effect, since we were unable to find any patient subgroup in which response to treatment varied directly with radiation dose.

A second possible explanation for the lack of dose response effect might be that there are differences between the treatment groups, other than the radiation dose, which significantly changed their response to treatment. However, when group differences were adjusted for age, KPS, histology and extent of surgery, there were no significant differences in time to tumor progression or survival among the three treatment groups, as indicated in Table 3. In addition the number of patients who did not complete radiation therapy or who did not receive CCNU at the time of tumor progression were comparable in the three treatment groups.

In summary, we could not find any factors which might account for a lack of dose response and therefore we conclude that, at least in our patient population, there was no dose response effect. In this respect our study is comparable to RTOG 83-02, which did not demonstrate a dose-response effect.

Comparison to other clinical trials in patients with malignant glioma

Times to tumor progression and survival for our

Table 7. Acute skin toxicity (numbers of patients)

	6141 cGy		7120 cGy		8000 cGy	
	N	(%)	N	(%)	N	(%)
No toxicity	75	(75)	48	(66)	37	(35)
Slight erythema	9	(9)	8	(11)	32	(30)
Brisk erythema	9	(9)	12	(16)	24	(22)
Moist desquamation	7	(7)	5	(7)	14	(13)
Total	100		73		107	

Table 8. Late CNS radiation toxicity autopsy results

	6141 cGy N	7120 cGy N	8000 cGy N
Deceased patients at risk*	82	55	79
At risk patients autopsied	12	9	10
Residual tumor	12	9	10
Evidence of CNS radiation effect in addition to residual tumor	2	1	0

* Patients considered at risk for late CNS radiation effect were those who survived at least 3 months after completion of radiation treatment. All other patients died during or within 3 months of completion of radiation therapy.

patient population were generally shorter than those reported in the literature for patients with malignant glioma [20, 21]. Winger *et al.* [22] showed that survival predictions for patients with malignant glioma may be overly optimistic because of selection bias in trials conducted at major medical centers. Patients entered in such trials are preselected prior to referral to such centers and are generally younger and less disabled than non-study patients. Our patient population is not comparable to such a pre-selected study group since it consisted of all patients with malignant glioma from a population of 2.5 million aged from 18 to 70 with Karnofsky performance status greater than 30. Therefore we expected that time to tumor progression and survival for our patient group would be less than those reported in the literature. Median survival for our patient group was comparable to a similar unselected group of patients with malignant glioma treated at a regional cancer center comparable to the two cancer centers where our patients were treated [23].

Interstitial implantation of radioactive sources (brachytherapy) may prove to be an effective modality for the initial treatment of patients harboring primary malignant glioma. Larson *et al.* [24] reported preliminary results of a study currently underway in San Francisco in which, following surgery, patients are randomized to treatment with either external beam radiation therapy plus chemotherapy or the same treatment plus brachytherapy. Median survival of patients with glioblastoma multiforme treated with external beam radiation therapy plus chemotherapy was 52 weeks compared to 95 weeks for those given the same therapy plus brachytherapy. Median survival of patients with anaplastic astrocytoma treated with external beam radiotherapy plus chemotherapy was 165 weeks compared to 223 weeks for those given the same treatment plus brachytherapy. These results are clearly superior to ours. However, only a highly selected group of patients are suitable for brachytherapy; namely, those with single, small (less than 5 to 6 cm diameter) well circumscribed tumors. Patients are usually younger, with KPS of at least 70. In our entire patient population, only seven of 78 patients with anaplastic astrocytoma (9%) and nine of 202 patients with glioblastoma multiforme (4%) would have been eligible for brachytherapy. Thus our patient population comprises a group with poorer prognostic factors who are not comparable to those treated with brachytherapy.

Radiation induced brain toxicity

We were able to administer a higher dose of radiation in a shorter period of time using hyperfractionation, with no significant increase in late delayed neurotoxicity as the dose of radiation was increased.

Sheline [3] introduced the term neuret to allow comparison of patients given different total doses of radiation to the brain utilizing different numbers of fractions over different periods of time for the purpose of estimating the risk of radiation induced brain necrosis. He estimated that the incidence of brain necrosis would be less than one percent with neuret doses less than 1000.

The neuret equivalents for the treatment given to our patients were calculated using Sheline's formula [3]: neuret = $D \times N^{-0.44} \times T^{-0.06}$ where D is the radiation dose in cGy, N is the number of fractions, and T the total treatment time in days. For patients treated to a dose of 6141 cGy according to protocol, the dose given to the region of the tumor plus surrounding peritumoral edema plus a 2.5 cm margin was 776 neurets. Patients treated on the 7120 cGy arm received 834 neurets and patients treated on the 8000 cGy arm received 937 neurets to the tumor and surrounding region. For patients treated on the 6141 cGy and 7120 cGy arms, the dose received by the remainder of the brain was 628 neurets and for patients treated on the 8000 cGy arm the dose received by the remainder of the brain was 666 neurets.

The low incidence of radiation induced brain toxicity is not unexpected according to Sheline's review [3]. All our patients received less than 1000 neurets to the area of brain receiving the highest dose of radiation. Although Sheline cautions that his predictions have not been confirmed for patients treated using hyperfractionation technique, our results suggest that higher radiation doses than

were used in our study could be given using hyperfractionation technique without a major increase in the incidence of radiation necrosis, at least over the survival period of our patient population.

Prognostic variables

Age, Karnofsky performance score, extent of surgery and tumor histology are significant prognostic factors which are of value in predicting the outcome of treatment in patients with malignant glioma.

In this study age was the most significant variable in predicting both time to tumor progression and survival.

When assessed with the Cox proportional hazards, multivariate analysis, KPS was highly significant in predicting survival, but not tumor progression. This observation needs to be confirmed by other studies, but suggests that the clinical variables traditionally used to predict treatment outcome may have different prognostic value in predicting time to tumor progression compared with survival.

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